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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/266,803	03/12/1999	GREGORY M. GLENN	PM-256865	6258

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EXAMINER
EWOLDT, GERALD R

ART UNIT	PAPER NUMBER
1644	36

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/266,803	Glenn et al.
Examiner	**Art Unit**
G.R. Ewoldt, Ph.D.	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 18, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-35 and 50-111* is/are pending in the application.

4a) Of the above, claim(s) *78* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-35, 50-77, and 79-111* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 31
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: ~~Notice to Comply~~

DETAILED ACTION

1. Applicant's amendment and remarks, filed 3/18/03, are acknowledged.

2. Claims 30, 62-77, 104 and 107 have been rejoined. Accordingly, this Office Action has not been made final.

Claims 1-35, 50-77, 79-111 are under examination.

3. The corrected drawings have been found acceptable by the Examiner.

4. In view of Applicant's Amendments and Remarks, filed 3/18/03, only the following rejections remain. The rejections under 35 U.S.C. § 103(a) have been withdrawn for the following reasons. The rejections relying on U.S. Patent No. 5,340,588 have been withdrawn because the reference teaches encapsulation of the immunizing formulation by liposomes whereas an antigen encapsulated in any way by a liposome has been specifically excluded from independent Claim 31 and all dependent claims. Given the addition of the new limitation regarding application of the instant formulation to hydrated skin, the rejections relying on Paul et al. have been withdrawn because the reference teaches the application of the immunizing formulation to dry skin.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-35, 50-77, and 79-111, stand/are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, "toxin or a derivative thereof," (claims 22-24).

Applicant's arguments, filed 3/18/03, have been fully considered but have not been found persuasive. Applicant argues "Support for derivatives of a specific bacterial ADP-ribosylating exotoxin (e.g., PT, CT, LT, DT, ETA) is found inter alia on pages 16-18 of the specification and were known in the prior art although not disclosed to be useful for transcutaneous immunization." Applicant continues "As taught by Applicants in their specification, the separate functions of A and B subunits and the ability to separate functions (e.g., ADP ribosylation, receptor binding) enables one to make the derivatives recited in the claims. Such derivatives were available as of the effective filing date of this application (i.e., November 14,1996) and do not require further description in the specification. A specification need not teach, and preferably omits, what is well known in the art."

It is the Examiner's position that Applicant's post-filing arguments do not provide the adequate written description that is required to be present in the specification. It is noted that but a single derivative of a toxin comprising adjuvant activity is actually disclosed (CT B subunit) at pages 16-18 of the specification. The bulk of the disclosure at pages 16-18 relates to developing toxoids from toxins. Said toxoid might be considered to be adequately described, however, said written description is not adequate for the much broader "derivatives" recited in the claims.

Regarding Applicant's last assertion that "A specification need not teach, and preferably omits, what is well known in the art," it is the Examiner's position that it is at least curious that Applicant would find it necessary to describe certain aspects of the invention, e.g., the buffers in which an antigen might be dissolved (which are clearly known in the art), in detail, yet then omit claimed limitations, i.e., a description of toxin "derivatives", and then argue that it is "preferable" to omit said description because it is known in the art. The position would not seem to be consistent.

7. Claims 1-35, 50-77, and 79-111, stand/are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed (note that the new matter portion of the claims in underlined), specifically:

A) an "antigen which is not encapsulated" (Claim 1),

B) the "method of Claim 1 wherein a physical, chemical, electrical, or sonic penetration enhancer is not used" (Claim 4),

D) "toxin or a derivative thereof," (Claims 25-26, 85-90, and newly added Claims 108-111),

E) and at least some "antigen which is not encapsulated" (Claims 31 and 32),

F) and at least one "antigen derived from a pathogen which is not encapsulated" (Claim 33),

G) the method of claim 31, "wherein the formulation comprises a genetically produced derivative of ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated" (Claim 51),

H) the method of claim 31, "wherein the formulation comprises a chemically produced derivative of ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated" (Claim 52),

I) a method wherein the antigen/molecule "is at least partially purified" (Claims 54-60 and 96-102),

K) The method of Claim 1/31, "wherein at least one adjuvant binds a receptor on antigen presenting cells" (Claims 82 and 93).

Applicant's arguments, filed 3/18/03, have been fully considered but have not been found persuasive. Applicant argues that support for the "pathogen which is not encapsulated" limitation can be found on page 20, lines 23-26 of the specification. Applicant also argues that the limitation is "implicit".

Applicant is advised that the disclosure regarding non-encapsulation by liposomes cannot support claims drawn to the more generic non-encapsulation in the absence of liposomes. Regarding the implicit argument, "implicity" is not a standard for patentability.

Applicant argues that support for the negative limitations of Claim 4, i.e., the specific absence of specific penetration enhancers can be found in the positive disclosure that generic penetration enhancers may be used. Said support is insufficient for the recitation of the specific negative limitations of the claims.

The rejection of Claim 15 has been withdrawn.

Applicant argues that support for the toxin derivatives can be found at pages 16-18. Said disclosure is insufficient, see Section 8, above for the Examiner's position regarding the recitation of "derivatives".

Applicant argues that support for the specific limitations of Claims 51 and 52 can be found in the generic disclosure at page 6 of the specification.

Applicant is advised that generic disclosures are generally insufficient support for specific limitations as is the case with Claims 51 and 52.

Applicant argues that support for the limitation of "partial purification can be found at page 17, lines 23-34.

Applicant is advised that no such specific limitation has been found anywhere at page 17.

The rejection of Claims 81 and 92 have been withdrawn.

Applicant argues that support for the limitations of Claims 82 and 93 can be found at page 16, lines 26-33.

Applicant is advised that no such specific limitations regarding all ADP-ribosylating exotoxin adjuvants has been found anywhere at page 16.

8. Claims 1-29 1-35, 50-77, and 79-111 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of inducing an immune response comprising hydrating intact skin and applying a formulation to intact skin of an organism, wherein the formulation comprises at least one ADP-ribosylating exotoxin adjuvant and an effective amount of an antigen derived from a pathogen,

does not reasonably provide enablement for:

A) a method of inducing an immune response comprising: applying a formulation to intact skin of an organism wherein the formulation comprises at least one adjuvant and an effective amount of an antigen derived from a pathogen, activating a Langerhans cell, and presenting at least one antigen or epitope thereof on a cell surface of the Langerhans cell to a lymphocyte (Claim 1).

B) a method of inducing an immune response comprising:

activating an antigen presenting cell, and presenting at least one antigen or epitope thereof on a cell surface of an antigen presenting cell to a lymphocyte (Claim 32).

C) a method of inducing an immune response comprising: activating a Langerhans cell, signaling the Langerhans cell to migrate to a lymph node, and presenting at least one antigen or epitope thereof on a cell surface of the dendritic cell to a lymphocyte (Claim 33), for the reasons of record set forth in Paper No. 30, mailed 10/18/02.

Applicant's arguments, filed 3/18/03, have been fully considered but have not been found persuasive. Applicant argues "Applicants submit that their teaching should be accepted as objectively true in the absence of any evidence or reasoning which is inconsistent with the proposed mechanism." Applicant further argues, "If this rejection is maintained, the Examiner is respectfully requested to cite authority for his assertion or, in the absence of legal authority contradicting *Marzocchi*, to make "acceptable evidence or reasoning" of record which is inconsistent with claims 1 and 32-33." Applicant further argues, "Finally, the Examiner did find that the specification was enabling for "a method of inducing an immune response comprising hydrating intact skin and applying a formulation to intact skin of an organism, wherein the formulation comprises at least one ADP-ribosylating exotoxin adjuvant and an effective amount of an antigen derived from a pathogen." Applicants submit that at least independent claims 30-31 and 62 as well as claims depending therefrom are enabled in accordance with the Examiner's finding.

Applicant is advised that the rejection, as set forth in the last action, adequately disclosed why the rejection was made. Both proper scientific reasoning, and references supporting said reasoning, were made of record. It remains the Examiner's position that Applicant's assertions regarding the mechanisms by which the admittedly highly unexpected results have been achieved are themselves highly unexpected and highly unpredictable. It remains the Examiner's position that mere assertions as to mechanisms are insufficient. Note that in Applicant's instant argument, submitted *nearly 7 years* after the instant specification's priority date, the best Applicant can say about the asserted mechanism is, "A mechanism by which the claimed invention *may* induce an antigen-specific immune response is taught on page 3, line 35, to page 4, line 6, of the specification" (emphasis added by Examiner). Clearly, Applicant is even now still unsure as to how the instant invention

functions. Accordingly, the rejection is proper and has been maintained.

Regarding Applicant's final assertion that Claims 30-31 and 62 as well as claims depending therefrom are enabled in accordance with the Examiner's finding, Applicant is simply in error as several of the limitations of the claims are not enabled.

9. The following are new grounds for rejection.

10. Claims 30, 62-77, 104, and 107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of inducing an immune response comprising hydrating intact skin and applying a formulation to intact skin of an organism, wherein the formulation comprises at least one ADP-ribosylating exotoxin adjuvant and an effective amount of an antigen derived from a pathogen,

does not reasonably provide enablement for:

a method of inducing an immune response comprising applying an adjuvant only.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding *in vivo* methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature

of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the biological arts are such that no methods of inducing an immune response, absent an antigen (as would be encompassed by the instant invention as broadly claimed), are currently known.

An immune response can be defined as a response to an antigen (see Stites et al., 1987). Accordingly, an immune response in the absence of an antigen (an embodiment that would be encompassed by the method of the instant claims) would seem to be impossible. Given said impossibility, the claimed method must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples (i.e., any working examples in which an immune response is demonstrated in the absence of an antigen), the unpredictability of the art, and the breadth of the claims (particularly as they encompass an impossible embodiment), it would take undue trials and errors to practice the claimed invention.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Technology Center 1600 at 703-872-9306 (before final) and 703-872-9307 (after final).

G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600
May 19, 2003